IV: VACCINES

AREA OF EMPHASIS:

Vaccines

SCIENTIFIC ISSUES

Research on ways to control the AIDS global pandemic remains a top priority for the NIH. HIV vaccines are a key component of this research because prophylactic vaccines could work in one of several ways to prevent AIDS: to prevent HIV infection, to prevent disease, and/or to prevent transmission. Over the past 8 years, the NIH has increased support for a broad program encompassing basic, preclinical, and clinical research on HIV/AIDS vaccines to its current level at more than four-and-a-half times the budget allocated in FY 1996. The first efficacy trials of candidate vaccines composed of bivalent recombinant gp120 envelope proteins with alum adjuvant were successfully completed in North America and in Thailand by a biotechnology company in 2002–2003. These trials tested one of the first HIV vaccine concepts proposed and, unfortunately, these candidate vaccines, which relied primarily on the ability to induce neutralizing antibody directed against the outermost envelope component of HIV, failed to provide evidence of protection against HIV infection. This failure to provide protection appears to be related to the limited breadth of the virus neutralization response induced by these and other gp120 vaccines. Additional analyses of trial data and samples from this and related clinical trials conducted by the NIH may provide clues to guide future studies. As a result of increased funding from the NIH in the area of basic vaccine research in AIDS, many new approaches to HIV vaccines are being studied in preclinical testing in animal models, and a second generation of products that induce cellular immune responses to one or

more components of the virus are approaching advanced levels of testing in clinical trials. Because of experience developed with some of the initial HIV vaccine candidates, new candidate HIV vaccine products are being developed more rapidly for clinical use. Up to 10 additional products or combinations of candidate vaccine products are expected to enter Phase I and/or Phase II safety and immunogenicity trials in human volunteers during the next 2 years, reaching decision points for efficacy trials within 3 to 4 years. With the number of trials already ongoing, this will put a strain on the existing network of domestic and international sites currently conducting trials. More companies and more organizations are involved in HIV vaccines than ever before, and issues of coordination and cooperation have become an important component of the HIV vaccine agenda. As promising candidates move further in the HIV vaccine pipeline, it will become increasingly important to expand the trained core of personnel who are able to conduct HIV vaccine trials and to train interested and committed individuals in their communities to educate and counsel individuals who are at increased risk for HIV infection, whether or not they enter HIV vaccine trials.

Vaccine Design

Basic research on the virus and on the human immune responses to HIV infection continues to provide the crucial foundation for the design and development of novel AIDS vaccine candidates. Building on the insights of recent basic research findings on the structural components of HIV, particularly those related to the HIV envelope, and studies on immune responses in small animals and nonhuman primates (NHPs), new vaccine candidates are being designed and tested. One of the major hurdles that has faced HIV vaccine design is the genetic diversity of HIV, particularly in the HIV envelope. To address the issue of HIV diversity, vaccine candidates are being constructed based on isolates from many regions of the world, and several research groups are exploring mixtures of viral components from different isolates and clades. Other groups are attempting to identify natural variants that express conserved envelope epitopes for neutralization that are seen on a wide range of strains. Antigens or epitopes are being expressed on conformationally appropriate trimeric envelope structures. In addition, concepts that generate genetic copies of HIV that represent either a consensus of the genetic sequences for some HIV subtypes or ancestral HIV for the main, M group of HIV-1 strains are being explored. Others are seeking to identify or develop HIV envelope structures or mimics which either expose selected critical epitopes or are more broadly immunogenic than the original constructs of envelope gp120 that have been tested in clinical trials. Important new information about

the envelope proteins of the first viruses to grow out in infected individuals may provide new focus for envelope vaccine design and evaluation. Recent information about the processing of internal structural components (gag) offers new ways to inactivate the virus and add safety features to HIV vaccines. In addition, several newer vaccine strategies are exploring different adjuvants, immune modulators, and other delivery components to optimize the immune responses that are generated by the HIV vaccine candidates. Basic studies on the mechanisms of antigen presentation, rules of engagement of both innate and adaptive immune responses, and design of vaccines to engage the most effective antigen presentation are ongoing.

Animal Model Development and Testing of Vaccines

Suitable animal models, especially NHPs, are crucial to further development and preclinical testing of new concepts in HIV/AIDS vaccine candidates. The NIH has made a considerable investment in the expansion of macaque colonies and appropriate biosafety housing to ensure their availability for proof-of-concept studies for HIV vaccines as well as other important pathogenesis and microbicide research. Because HIV does not replicate in monkeys without adaptation, simian immunodeficiency viruses (SIV) or recombinant chimeric simian-human immunodeficiency viruses (SHIV) with HIV envelope inserted into an SIV backbone have been used in vaccine studies involving HIV envelope. The initial pathogenicity and vaccine studies with SHIVs have revealed a number of limitations, and newer versions of this type of recombinant or chimeric virus are now being studied for pathogenicity and infection by different routes. One of the primary concerns is that some of the highly pathogenic recombinant SHIVs do not reflect the normal slow progressive loss of CD4 T cells seen in HIV-infected persons. Thus it appears easy for vaccines to induce immune protection from disease progression with even a modest impact on the initial viral replication of SHIV strains. Unfortunately, the SIVs, which more closely mimic HIV disease progression, do not permit direct evaluation of candidate HIV vaccines that incorporate HIV envelope components. Newer SHIV stocks, which have been derived from recently transmitted HIV or HIV isolates using CCR5 chemokine receptors that are classified as macrophage-tropic, are now being studied. In addition, SHIV strains that reflect the kinds of viral diversity seen in the global epidemic are being constructed and tested to prepare viruses for testing of vaccine strategies that incorporate diverse HIV envelope components. Several groups have been developing animal models to address questions of repeated low-dose mucosal exposure and mother-to-child transmission (MTCT) of HIV. The latter may serve both as models for passive immunity to address neonatal transmission and as infant models to address questions of vaccine-induced prevention of breastfeeding transmission.

Correlates of Immune Protection

AIDS vaccine research with at least limited protection using monkey models has provided strong scientific rationales to further explore and develop several vaccine concepts and to move additional vaccine candidates into clinical testing. However, there is, as yet, no single correlate of immune protection that can be used as a yardstick to compare the kinds of protection observed in different animal models. As research on HIV/AIDS vaccines progresses, evidence is accumulating that the correlate of protection will be some complex of both cellular and humoral immunity that may not be measured by assays currently employed. In parallel, additional basic research is needed to better understand what makes some individuals either resistant to infection when they are exposed to HIV or able to control the infection so that disease progression is slowed even without the use of antiretroviral therapy (ART). While some individuals with specific major histocompatibility genotypes are able to mount strong protective immune responses, it is not clear whether vaccine candidates can similarly induce and maintain these kinds of responses in the broader population at risk of infection. Also it is not clear which components of these immune responses are necessary and sufficient for protection. This poses a need to move candidate vaccines into human clinical trials to obtain some of these answers.

Clinical Trials and Site Development

Over the past 6 years, the HIV Vaccine Trials Network (HVTN) has expanded from a small number of domestic sites conducting Phase I and II vaccine trials that were present in the AIDS Vaccine Evaluation Group (AVEG) to a network, now consisting of 17 domestic and 15 international sites for the conduct of Phase I, II, and III clinical trials. Significant efforts are underway to identify populations and develop cohorts necessary to conduct large-scale clinical studies at these and additional sites. In some cases, these sites require substantial infrastructure development and capacity building to ensure that the clinical researchers, scientists, and medical personnel are appropriately trained to design, conduct, and analyze the clinical trials as full and equal partners. In addition, the active education and full participation of the affected community in these efforts also is critical and must be built in parallel.

The NIH has now conducted, in collaboration with academic researchers and industry cosponsorship, more than 60 Phase I and 3 Phase II clinical trials of more than 30 vaccine products, individually or in combination, in human volunteers. Although production of some new candidate vaccines for clinical study has proceeded slowly, more than 10 new candidate vaccines

have entered clinical trials sponsored by the NIH in the past 18 months and at least 10 additional new products will enter Phase I trials during the next 2 years. Several new combinations of products, which are expected to provide even better immune responses in combination, will also be tested in Phase I or II trials. Initial studies are leading to more complex vaccine candidates that may provide better protection from HIV transmission. The Dale and Betty Bumpers Vaccine Research Center is evaluating the immune responses from its first Phase I clinical trial of a multiclade, multigene DNA vaccine candidate. Sites in Haiti, Trinidad and Tobago, Brazil, and Peru jointly have completed a Phase I study that was conducted in parallel with studies in the United States and are initiating studies with newer candidate vaccines. Sites in Botswana and South Africa initiated Phase I trials of new products in 2003 in parallel with studies in selected sites in the United States. Other international sites are conducting studies of seroincidence to assess the feasibility of trials in selected populations. In partnership with the Government of Thailand and the U.S. Department of Defense, Walter Reed Army Institute of Research (WRAIR), the NIH is supporting a large communitywide Phase III trial of the "prime-boost" concept utilizing an avipox recombinant vector (ALVAC - vCP1521) to prime the T-cell components of the immune response to several HIV proteins and a bivalent B/E recombinant gp120 envelope protein product (AIDSVAX B/E) to boost immune responses to the envelope.

It is anticipated that nearly all of the second-generation vaccines will be focused on induction of cellular immune responses to control viral load and disease progression with limited breadth of antibody protection against genetically diverse infections. Therefore, the NIH will continue to place a high priority on the development and testing of AIDS vaccine candidates and provide support for the basic research and preclinical testing needed to continue to resolve this gap in the AIDS vaccine pipeline.

FY 2006 PRIORITIES FOR HIV/AIDS VACCINES

Several priority areas previously identified in the *FY 2005 NIH Plan for HIV-Related Research* have been revised and modified or focused to more specifically address the most critical needs.

PRIORITY FOR FUTURE RESEARCH:

- **Maintain a strong NIH research portfolio to ensure a continuing vigorous program of basic and preclinical research for discovery, preclinical evaluation, and introduction of new vaccine candidates and immunization concepts. This remains a key overarching priority that needs to be balanced with the urgency to develop and test existing HIV vaccine candidates in domestic and international cohorts.**

Vaccine candidates now in clinical trials or even in current product development are unlikely to achieve the goal of a highly effective HIV vaccine. Indeed, we presently are faced with the failure of the first large Phase III trials to provide broad neutralizing antibody protection against HIV infection. The ongoing Phase III trial and the next proof-of-concept trials of candidate HIV vaccines are likely to be focused on induction of cellular immunity. Based on preclinical data in animal models, these vaccine candidates are more likely to delay disease progression than prevent HIV infection. Thus, urgency exists to pursue additional, more highly effective vaccine designs to prevent HIV infection through continuing support for Innovation Grants (R21) and HIVRAD (R01 or P01) programs to provide a strong research base for continual development of new vaccine concepts.

PRIORITY FOR FUTURE RESEARCH:

- **Emphasize support for basic vaccine design research, particularly innovative research on immune responses to HIV envelope to address the issues related to improvement in the strength and breadth of the humoral immune response.**

It is critically important to continue to devise vaccine candidates that might be able to induce broadly cross-reactive HIV-neutralizing antibodies that will deal with the diversity of HIV clades and circulating recombinant forms of HIV. Passive antibody transfers in animal models have demonstrated the potential protective effect of high-titer antibodies to HIV. Current candidate HIV vaccine products in development or early testing may be yielding incremental progress toward this elusive goal. However, innovative approaches to induce high-titered antibody responses that prevent infection should be pursued as a top priority in this HIV vaccine research.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to support basic research on the identification of correlates of immune protection: study the development and maintenance of effective immune responses to HIV antigens, particularly at mucosal surfaces, and address issues related to improvement in the duration of potentially protective immune responses.**

It is critically important to continue to investigate host responses that are able to control HIV infection and to study strategies to induce long-lasting, vaccine-induced immune responses that impair the ability of HIV to establish infection at the sites of transmission or that impair viral replication and dissemination. Several scenarios now have been reported with vaccination

or controlled virus exposure in animal models where several previously proposed correlates of immunity (cytotoxic T lymphocytes [CTLs], interferon gamma-producing cells, or neutralizing antibodies) have not been observed. Current candidate HIV vaccine products in preclinical development and in clinical trials may provide some additional information on these kinds of novel responses and the means to measure them. However, a comprehensive, concerted effort to identify correlates of immune protection in the "exceptions" should be examined, and the means to optimally induce and measure these responses should remain a high priority of HIV research for the NIH.

PRIORITY FOR FUTURE RESEARCH:

- **Implement direct "head-to-head" and comparative studies to assess immune responses in both preclinical and clinical evaluation of HIV vaccine candidates. Appropriate reagents, assays, and animal models should be developed and the information and reagents shared widely to facilitate comparative vaccine studies. This includes development, identification, selection, and production of virus stocks for shared use in widely accepted animal NHP models. To ensure comparability, expanded assessments of cellular immunity and neutralizing antibodies in central laboratories using validated assays and broader access to specimens are encouraged for both academic and industrial investigators.**

Data from several animal models, where protection either has been achieved or has failed, indicate that current assays for vaccine-induced CTLs or antigen-specific gamma interferon induction by CD8+ T cells are not predictive of protection from immunodeficiency disease endpoints. The urgent need to develop improved or alternative chimeric SIV/HIV–SHIV models that more closely mimic human HIV infection has been recognized, and the NIH should support efforts to generate new stocks and make them widely available as soon as possible. Other concerns about the development of an array of similar or related vaccine candidates with little or no comparative data among products often leaves the NIH with a limited basis on which to select and move one or more products into clinical testing. Tests for neutralizing antibodies often are analyzed with only a few clinical isolates that are available to an individual investigator or company. New, quality-controlled panels of virus isolates and/or viral pseudotype assays should be made available to HIV vaccine investigators to improve the ability to compare and optimize vaccine candidates. NHP studies are not required by the Food and Drug Administration (FDA) for movement of products into Phase I clinical testing, but strong

immunogenicity in humans and proof-of-concept protection in NHPs will undoubtedly be a driving force to move products beyond Phase I trials in human testing. Thus, access to NHPs for comparative study and testing in appropriate models is essential as early as possible in vaccine testing so that these studies can be integrated with decisionmaking for human trials.

PRIORITY FOR FUTURE RESEARCH:

- **Improve the linkage of vaccine design efforts with the clinical trial networks and cohorts being developed for clinical trials to better integrate the animal model data into human vaccine trial planning and to inform all stakeholders. Conduct appropriate preparative work in trial sites, particularly in international sites and minority communities, to provide critical viral and immunological information to inform vaccine trial design while helping to develop strong, sustainable research infrastructure.**

Through the HVTN and other mechanisms, the NIH, in coordination with other agencies (through Partnerships for AIDS Vaccine Evaluation) and organizations (the HIV Vaccine Enterprise), plans to support pretrial infrastructure to assess incidence and immune responses to regionally and temporally acquired HIV isolates. Additional studies in natural history for information about viral load endpoints, normal values for clinical biomarkers, background vector immunity in the population, information about comorbidity, and other relevant health factors will enable training in laboratory experimentation and development of a cadre of investigators with experience in vaccine-related biomedical research. Further linkage of vaccine basic research and newly developing scientific and clinical infrastructure at sites as quickly as possible is desirable so that basic research questions related to HIV epidemiology and transmission, as well as vaccine design and development, are appropriate for the sites involved and provide training for a broader, more sustainable research infrastructure.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and implement a defined plan with specific goals to educate high-risk populations and communities in the United States and at international sites about HIV vaccines. In particular, continue to develop tools, devise outreach programs, and implement strategies to involve minority populations as well as international populations in HIV vaccine trials that will be testing products for efficacy.**

Health disparities exist at many levels in the United States and even more so in the international arena. Vaccine studies supported by the

NIH need to address the increasing burden of HIV infection observed in minority populations in the United States and the increasing burden of infection in young women worldwide. Because some of the highest risk populations for HIV infection are adolescents and young adults, minorities, and women, it is imperative that HIV vaccine trials be inclusive of all populations where benefit might be derived. In addition to broad outreach and community education, the NIH needs to develop and implement a plan with specific goals to achieve an understanding of the potential benefits of a vaccine trial in at-risk communities. Because it will take time to establish trust in many of the highest risk communities, efforts to engage young people in these populations must begin now. There appears to be great value in conducting Phase I trials in selected populations, particularly in the international sites where future large-scale vaccine trials will be conducted. Preparation and conduct of HIV vaccine trials also will train a core of individuals who will be training the next generation of clinical vaccine researchers. This kind of effort should be conducted in parallel in domestic sites to encourage young minority investigators to bridge vaccine trial efforts with improved public health in their communities.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

STRATEGIES:

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other lentiviruses by pursuing research that includes the following areas of interest:
  - Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific and antigen-nonspecific cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - Define the structure-function relationships and the antigenicity and immunogenicity of HIV proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active and passive immunity.
  - Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and related lentiviruses evade or escape from humoral and cellular arms of the immune response; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
    - Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by major histocompatibility complex (MHC) class I and class II molecules. Investigate the interaction of HIV proteins with antigen-processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.

- Study the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease and in response to vaccination; define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and related viral antigens, and development of long-term protective immunity, particularly in human subjects.
- Study the mechanism of action of vaccine adjuvants and enhanced modes of HIV and related lentivirus antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out translational research in NHP and human vaccines.
- Determine how chronic infection with one strain of HIV or related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain; define the properties of the virus and of the immune system that are responsible for lack of disease induction by attenuated viruses and protection from challenge with wild-type virus; and determine the protective mechanism, duration, and extent of cross-protection.
- Define the heterogeneity of specific responses to vaccine immunogens, particularly HIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral exposure.
- Determine which factors promote development of particular human effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific protective mechanisms.
- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.

- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

- Seek new clues for correlates of immune protection from HIV-infected or highly exposed but seronegative individuals, across the lifespan, and from lentivirus models that will provide the basis for further design of candidate vaccines by conducting the following research:

  - Study acutely infected individuals, exposed/seronegative, or possibly transiently infected humans (including uninfected children born to HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and nonprogressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) that reduce the amounts of circulating virus and influence disease course.

  - Elucidate the functional mechanisms for protective immunity against HIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.

  - Investigate the sequence of events required for mucosal transmission/infection of HIV and other lentiviruses at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.

  - Study mucosal immunity to viral antigens and other infectious pathogens in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.

  - Explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1; acquire clinical specimens from populations relevant to vaccine trials for laboratory studies; and acquire appropriate epidemiological information to enable interpretation of these analyses.

- Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, human papillomavirus (HPV) and other infectious diseases, and with administration of drugs of abuse or effects of ART on viral shedding in vaccinated subjects. Model these confounding elements in NHP.

- Develop *in vitro* experimental approaches for analysis of vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across lifespan) and protected animals by undertaking the following research activities:

  - Develop and improve animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by a genetic sequencing, particularly of selected regions of the macaque genome.

  - Develop improved methodologies and assays to measure viral neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary isolates.

  - Develop and standardize immunological reagents; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, storage, recovery, viability, shipping, and tracking of samples that will be essential in large-scale trials.

  - Study the function of CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary virus isolates; and make available those reagents required for vaccine-related studies.

- Develop or improve sensitive quantitative measures of HIV (and SIV) in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE - B:

Design viral antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernmental organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations.

STRATEGIES:

- Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
  - Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
    - Virus-like particles containing one or more virus proteins, peptides, or antigens;
    - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - DNA or RNA coding for viral proteins;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
    - Viral replicons or other strategies to target DCs;

  - Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;
  - Structurally constrained HIV envelope fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
  - Cell surface components carried on the viral surface.

- Foster collaboration between academic investigators, industry sponsors, the NIH, the FDA, other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should:
  - Enable production of pilot lots of vaccine candidates for testing in NHPs and human subjects;
  - Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
  - Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration among, academic investigators, industry, affected communities and populations, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include:
  - Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different components of the immune response; and
  - Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase breadth of immune responses.
- Support design, development, and incorporation of methods to improve or modulate immune responses (qualitatively or quantitatively) in vaccine approaches, including:

- Novel adjuvants and delivery methods that might enhance effective DC antigen presentation;
- Agents that stimulate or modulate mucosal immune responses or other host defenses, including cytokines or chemokines;
- Vaccines formulated with cytokines or incorporating cytokine genes in vectors or other biologically active molecules; and
- Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on vaccine responses.

• Evaluate the efficacy of vaccine and other immune prevention strategies in animal models of HIV and related lentiviruses by:

- Testing vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
- Determining *in vitro* correlates of an *in vivo* protective immune response;
- Determining the effect of vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious virus challenge on the effectiveness of the vaccine-induced immunity;
- Defining the impact of different vaccine approaches on kinetics of immune responses, kinetics and localization of viral replication, long-term followup of disease progression with low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
- Determining the impact of genetic factors and age on vaccine responses and on protection against virus at various challenge sites;
- Studying the efficacy of the immune response in the face of viral mutation and variation; and
- Investigating vaccines and other biomedical prevention strategies with attention to potential cofactors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormone replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune system and inflammatory activity that might compromise integrity of the mucosal surface or the inductive ability of vaccines.

- Support development of reagents and standardized methods to assess specific vaccine-induced immune responses in animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization and those due to viral infection;
  - Characterizing and evaluating the potential negative side effects of candidate vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in animal models;
  - Standardizing and validating assays to assess vaccine potency;
  - Standardizing and validating assays to be used as Phase III study endpoints; and
  - Abiding by Good Laboratory Practices (GLP) regulations to perform endpoint assays in support of product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with regulations stated in 21CFR part 58 and part 11.
- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development:
  - Whose production utilizes human-derived tumor cell and other continuous cell lines;
  - That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
  - That might have the ability to be generated as either replicating or nonreplicating vectors;
  - That have the potential to cause autoimmunity or highly immunogenic antivector responses; or
  - That overexpress potentially deleterious vector proteins.

OBJECTIVE - C:

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

STRATEGIES:

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - Develop relevant animal models of maternal-fetal and maternal-infant perinatal transmission that can:
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in primates;
    - Determine safety of various monoclonal and polyclonal antibody preparations;
    - Determine the best immunization routes or protocols to induce antibodies in milk and other secretions;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of antiviral drugs in combination with immune and behavioral prevention strategies.
  - Determine virologic and nonimmunologic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes:
    - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what viral factors are associated with differences in perinatal transmissibility;

        - Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervicovaginal secretions and in breast milk to determine their potential relevance in MTCT; and
        - Determining if virus in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
    - Identify maternal and infant immune responses that might control viral replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.

- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:
    - Determine specific immune strategies for perinatal intervention that blocks interaction of HIV with its receptors and coreceptors and/or to target infected cells.
    - Characterize the transmitted viral strains and monitor changes that may occur in proposed trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
    - Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns exposed to HIV (born to HIV-infected women).
- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:
    - Identify and characterize the important issues to consider in the development of criteria for advancement of candidate vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria should include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children.

- Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).
- Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- Develop criteria to define infant infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
- Study viral isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
- Study the impact of early ART interventions and HIV vaccines given while on effective ART, on the maintenance or regeneration of antiviral immune responses of HIV-infected infants.

OBJECTIVE - D:

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate vaccines or concepts in domestic and international settings.

STRATEGIES:

- Support the conduct of Phase I, II, and III clinical trials that will determine long-term and short-term safety, evaluate efficacy, and compare immunologic responses to different preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters. This includes the following:
  - Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should determine safety, test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of the general populations (gender, age, ethnic and racial minority) and populations affected by HIV, and be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger "proof of concept" or efficacy trials.
- Develop a comprehensive plan for conducting vaccine trials with a high level of retention and adequate followup of vaccinees to reach predefined endpoints, as follows:
  - Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the correlates of immune protection, long-term safety, behavioral factors to influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - Conduct collaborative large-scale efficacy trials of preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by:
    - Evaluating HIV vaccine candidate efficacy against HIV infection, disease progression, and/or transmission;

- Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity;
- Ensuring that trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of the HIV disease;
- Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
- Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, and cultural backgrounds that will be involved in trials.

- Characterize the clinical course, immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.
- Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III trials and assist in providing solutions.
- Conduct behavioral risk assessment research during vaccine trials, particularly with Phase II and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in a vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.
- Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

OBJECTIVE - E:

Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other Governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts.

STRATEGIES:

- Identify and develop potential domestic and foreign sites with a high seroincidence and access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
  - Track the course of the epidemic by studying HIV incidence in cohorts of individuals with high-risk behavior to identify and monitor changes in the risk profiles and infection rates (seroincidence) of various populations in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and capable participants in vaccine trials.
  - Develop new laboratory diagnostic tools that can be adapted for high throughput to study new HIV infections and allow distinction between vaccinees and infected individuals.
  - Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of viral load, and disease progression.
  - Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected people representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.
  - Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials; development of laboratory infrastructure; standardization of

assays and development of panels of geographic-specific reagents composed of local, indigenous HIV+ and HIV- samples as well as peptide reagents to serve as controls when validating and standardizing assays that will be used in support of clinical trials in that region; and participation of trained personnel in studies related to the trial.

- Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; listen to and address community concerns and social issues, and ensure ethical conduct of AIDS vaccine efficacy trials. This includes the following:

  - For all vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.

  - Develop mechanisms through CABs to engage collaboration and to provide education and the means to inform communities on a continuing basis so that social as well as medical concerns are addressed; work to establish trust in the community through open discussions of scientific rationale, expectations, and concerns.

  - For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), and the World Health Organization (WHO)/Joint United Nations Programme on HIV/AIDS (UNAIDS) to prepare for, plan, and conduct vaccine trials adhering to the highest ethical and scientific standards.

- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of a research trial. This includes the following research:

- Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of vaccine efficacy.
- Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, unblinding, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the epidemic is expanding disproportionately.
- Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to adolescents and young persons who are engaging in high-risk behaviors.
- Collaborate with other U.S. Department of Health and Human Services (DHHS) agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with WRAIR, the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in international settings.
- Evaluate the impact of community-based participatory research in the acceptability of vaccine trials.
- Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where vaccine trials are conducted.
- Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.
- Determine optimal methods of achieving informed consent for vaccine efficacy trials.

- Explore innovative trial designs to improve efficiency of vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine or utilizing initially concordant negative couples at high risk or discordant couples). This includes the following areas of trial design research:
  - Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression and clinical outcomes, and the benefit of long-term followup.
  - Consider the impact of early ART on HIV infections in complex trial designs.
  - Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs; integrate research on vaccines against opportunistic infections, as appropriate.

FY 2006 OAR Planning Group for Vaccines

FY 2006 VACCINES PLANNING GROUP

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